UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/669,768	09/24/2003	Yuqiao Shen	ONYX1047-DIV	8135

37499 7590 01/15/2008

ONYX PHARMACEUITICALS, INC.
2100 POWELL STREET
12TH FLOOR
EMERYVILLE, CA 94608

EXAMINER	
MARVICH, MARIA	
ART UNIT	**PAPER NUMBER**
1633	

MAIL DATE	DELIVERY MODE
01/15/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/669,768	SHEN ET AL.	
	Examiner	Art Unit	
	Maria B. Marvich, PhD	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10/15/07*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-13,24-28,33 and 35-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11,12,24,28,33,39 and 40* is/are rejected.

7)☒ Claim(s) *13,25-27 and 35-38* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 11-13, 24-28, 33 and 35-40 are pending in this application.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11, 12, 24, 28, 33, 39 and 40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of cancer characterized by p53 loss or deficiency by direct administration Onyx 051 and 053 (comprises a single amino acid substitution in amino acid 240 or 260), does not reasonably provide enablement for any other embodiment. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. **This rejection is maintained for reasons of record in the office action mailed 5/9/07.**

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). whether undue experimentation is required is not based on a single factor but is rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter, 1986) and In *re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

1) **Nature of invention**. The instant invention is drawn to recombinant adenovirus comprising single amino acid mutations in the E1B-55K gene such that binding to p53 is reduced as compared to binding between p53 and wild-type E1B-55K. The invention utilizes disciplines of molecular biology, virology and clinical technology.

2) **Scope of the invention**. Applicants' claims are broadly drawn to treatment using recombinant adenovirus *comprising any single amino acid mutation* in E1B-55K such that binding to p53 is reduced. Applicants' disclosure teaches development of two such mutants in which amino acid 240 and 260 are mutated to generate Onyx 051 and Onyx 053. These mutants are not able to bind to p53. As described in the specification, the method of the instant invention is directed toward treating cancer using the vectors and is based upon oncolytic replication function of the viruses in infected tumor cells.

3) **Number of working examples and guidance**. The instant invention is drawn to single amino acid mutations within E1B-55k that affect binding to p53. Applicants have constructed 26 mutant rAd in which a single amino acid within the E1B-55K coding sequence was mutated (see e.g. page 12, ¶ 4 and table 2). Two of these mutant R240A and H260A lost ability to bind p53 but did not lose late viral function. Furthermore, the cells were tested for oncolytic affect. U20S and Du145 cells were assayed and demonstrated that the two viruses were cytotoxic.

4) **State of Art**. Enormous efforts have been directed toward the development of vectors for cancer treatments. Adenovirus mutants that lack the ability to bind to p53 are replication deficient in non-replicating, non-neoplastic cells with p53 but in cells deficient in p53, the virus is replicative and oncolytic. Previously, the art has described generation of rAd comprising

deletions, substitutions and frame-shifts which inactivate the ability of E1B-55K to bind to p53 efficiently to generate E1B-p53- mutants. For example, ad2 dl1520 (Onyx 015) comprises a frame-shift mutation at nucleotide position 2022 that generates a stop codon 3 amino acids downstream of the AUG codon resulting in deletion of large region of E1B, US patent 5,677,178 describes the generation of rAd lacking E4orf6 and US 6,080,578 teaches construction of Onyx 019, 020 and 021 in which various amounts of internal sequences are deleted. Kirn et al teach that "the role of p53 in replication-selectivity of dl1520 has been difficult to confirm despite extensive *in vitro* experimentation by many groups, E1B-55K gene deletion was associated with decreased replication and cytopathogenicity in p53(+) tumor cells versus matched p53(-) tumor cells, relative to wild-type in RKO and H1299 cells" (page 6653, col 1, ¶ 3). Therefore, the efficacy of the instant adenovirus lies in treatment of p53 (-) tumors. This efficacy has been specifically observed when in combination with chemotherapy (see Kirn et al, page 6666, col 1).

5) **Unpredictability of the art**. The instant invention is unpredictable for treatment of cancer in humans given the broad recitation of a genus of adenovirus for delivery to p53 lacking neoplastic cells wherein the adenovirus have reduced binding to p53. The instant invention is based upon the premise that targeted mutations within E1B-55K result in a virus that is replicative in tumor cells lack p53 while normal cells do not. As well the specification teaches that this premise is distinctly connected to the replicative condition of the rAd. However, by recitation that the rAd comprises a single amino acid mutation in E1B-55K, the adenovirus to be used in the treatment encompasses a broad and diverse genus of adenoviruses that need only be linked by a mutation in E1B-55K. Rather the nature of the adenoviruses for treatment of cancer according to the instant invention must be replicative. To this end, applicants generated 26

mutants but only two of these mutants are capable of reduced binding to p53. These mutants (Onyx 051 and 053) comprise a single mutation in amino acid 240 and 260.

Hence, applicants have elucidated the unpredictability of any single amino acid to produce the required functional requirements as only two mutants of 26 produced have the recited functional requirements. As well, applicants have not provided the structural requirements of the single amino acid mutants such that one of skill in the art would be able to identify those mutants that have lost the ability to bind efficiently to p53. Hence, the unpredictability of using the claimed invention in gene therapy is accentuated due to the broad and unpredictable nature of the identifying adenovirus with single amino acid mutations in the E1B 55k gene that have lost the ability to bind p53 and furthermore be used to treat cancer.

6) **Summary**. In view of predictability of the art to which the invention pertains: undue experimentation would be required to practice the claimed methods with reasonable expectation of success, absent a specific and detailed description in the specification. Given the above analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be concluded that the skilled artisan would have had to have conducted undue unpredictable experimentation in order to practice the claimed invention.

Response to Argument

Applicants' arguments filed 10/15/07 have been fully considered but they are not persuasive. Applicants' claims are drawn to a method of treating a cancer characterized by neoplastic cells that substantially lack p53 function. The method requires use of an adenovirus

comprising a single amino acid substitution in the E1b gene wherein the adenovirus has reduced ability to bind to p53 and retains late function. The MPEP teaches, "However, claims reading on significant numbers of inoperative embodiments would render claims non-enabled when the specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative. Atlas Powder Co. v. E.I. duPont de Nemours & Co., 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984); In re Cook, 439 F.2d 730, 735, 169 USPQ 298, 302 (CCPA 1971). (see MPEP 2164.08(b). In the instant case, applicants recite use of a broad genus of adenovirus to treat cancer. The instant rejection is based upon the highly unpredictable nature of the claimed method of treatment of *any* cancer using *any* of a broad genus of adenovirus. The lack of guidance as to the molecules to be used exacerbates the highly unpredictable nature of treating cancer. While one of skill in the art can readily envision numerable species of nucleic acid sequences that have at least a single amino acid mutation in E1B 55k, one cannot predict which of these also generate an adenovirus that treats cancer.

The court and the Board have repeatedly held (Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.,18 USPQ2d 1016 (CA FC, 1991); Fiers v. Revel, 25 USPQ2d 1601 (CA FC 1993); Fiddes v. Baird, 30 USPQ2d 1481 (BPAI 1993) and Regents of the Univ. Calif. v. Eli Lilly & Co., 43 USPQ2d 1398 (CA FC, 1997)) that an adequate written description of a nucleic acid requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it, irrespective of the complexity or simplicity of the method; what is required is a description of the nucleic acid itself. It is not sufficient to define DNA solely by its principal biological property, because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any DNA with that biological property. Naming a type of material

generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. When one is unable to envision the detailed constitution of a complex chemical compound having a particular function, such as a nucleic acid, so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, i.e., until after the nucleic acid has been isolated. Thus, claiming all DNA's that achieve a result without defining what means will do so is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. Also, where a claim purports to cover all nucleic acids that encode a specific protein and the specification discloses but a single DNA known to do so, the situation is analogous to a single means claim and does not meet the enablement requirement under para. 1 of §112.

Applicants argue that two such mutants have been identified and methods provided for identification of other such mutants. However, the unpredictability of the instant methods are the result of the functional requirements of the broad genus of mutants in that they are required to be used in treating cancer by biding p53 and retaining late viral function. As to applicants arguments that "it is inappropriate for the Examiner to be questioning the scope of the presently claimed invention based on a question of whether or not one of the ordinary skill in the art is capable of "identifying adenovirus with single amino acid mutations in the E1 B 55k gene that have lost the ability to bind to p53", this statement omits the central issue at question which is in the remainder of the rejection "and furthermore be used to treat cancer". Applicants' results demonstrate that Onyx 051 and Onyx 053 in combination with chemotherapy can be used to

"treat cancer". Any other modalities for treating cancer would require undue experimentation to determine the parameters of treatment.

Conclusion

Claims 11, 12, 24, 28, 33, 39 and 40 are rejected.

Claims 13, 25-27 and 35-38 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. The claims are free of the art because the art fails to teach oncolytic adenoviruses that comprise single amino acid mutations at amino acid 240 or 26 (Onyx 053 and 051). Further, as explained above in the rejection made under 35 USC 112, first paragraph, the claims are drawn to the use of products that would result in therapeutic benefit due to ablated binding to p53. Onyx 053 and 051 are oncolytic viruses that exhibited ablated binding to p53 and lead to decreased cell growth in combination with chemotherapy.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

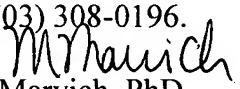
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B. Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (7:00-4:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, PhD can be reached on (571)-272-0739. The fax phone numbers for the organization where this application or proceeding is assigned are (571) 273-8300 for regular communications and (571) 273-8300 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.



Maria B Marvich, PhD
Examiner
Art Unit 1633